PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2 5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day month year) 15 May 2001 (15.05.01)	
International application No. PCT EP00 08361	**Applicant's or agent's file reference** LEA33861-WO
International filing date (day month year) 28 August 2000 (28.08.00)	**Priority date** (day month year) 08 September 1999 (08.09.99)
Applicant LERCHEN, Hans-Georg et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

05 March 2001 (05.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

BAYER AKTIENGESELLSCHAFT
51368 Leverkusen
ALLEMAGNE

Date of mailing (day month year) 20 March 2002 (20.03.02)	
Applicant's or agent's file reference LEA33861-WO	**IMPORTANT NOTIFICATION**
International application No. PCT EP00 08361	**International filing date** (day month year) 28 August 2000 (28.08.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
SCHULZE, Thomas Jakob-Böhme-Strasse 11 51065 Köln Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SCHULZE, Thomas-J 236 Quails Trail Thousand Oaks, CA 91360 Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3.

4.

[X]

[ ]

[X]

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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15 March 2001 (15.03.2001)

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WO 01/017563 A3

(51) International Patent Classification⁷: A61K 47/48

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(26) Publication Language: English

(30) Priority Data:
09/392,167 8 September 1999 (08.09.1999) US
09/606,772 29 June 2000 (29.06.2000) US

(71) Applicant *(for all designated States except US)*: **BAYER AKTIENGESELLSCHAFT** [DE/DE]; 51368 Leverkusen (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LERCHEN, Hans-Georg** [DE/DE]; Sürderstrasse 3, 51375 Leverkusen (DE). **BAUMGARTEN, Jörg** [DE/DE]; Henselweg 13, 42115 Wuppertal (DE). **BRÜGGEMEIER, Ulf** [DE/DE]; Leysiefen 20, 42799 Leichlingen (DE). **ALBERS, Markus** [DE/DE]; Edelrather Weg 154, 51375 Leverkusen (DE). **SCHOOP, Andreas** [DE/DE]; Siefen 3, 51491 Overath (DE). **SCHULZE, Thomas-J** [DE/US]; 236 Quails Trail, Thousand Oaks, CA 91360 (DE).

(74) Common Representative: **BAYER AKTIENGESELLSCHAFT**; 51368 Leverkusen (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report

(88) Date of publication of the international search report:
11 July 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/017563 A3

(57) Abstract: The present invention relates to [illegible] antagonists via preferred linking units. The preferred linking units guarantee serum stability of the conjugate of cytostatic and αvβ3 integrin antagonist and at the same time the desired intracellular action in tumour cells as a result of their enzymatic or hydrolytic [illegible] with release of the cytostatic.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
LEA33861-WO		
International application No.	International filing date *(day month year)*	(Earliest) Priority Date *(day month year)*
PCT/EP 00/ 08361	28/08/2000	08/09/1999
Applicant		
BAYER AKTIENGESELLSCHAFT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] it is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08361

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, CHEM ABS Data, MEDLINE, CANCERLIT, DISSERTATION ABS, EMBASE PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	KERR J S ET AL: "NOVEL SMALL MOLECULE ALPHAV INTEGRIN ANTAGONISTS: COMPARATIVE ANTI-CANCER EFFICACY WITH KNOWN ANGIOGENESIS INHIBITORS" ANTICANCER RESEARCH,HELENIC ANTICANCER INSTITUTE. ATHENS,.GR, vol. 19, no. 2A, 1999, pages 959-968, XP000924849 ISSN: 0250-7005	1-22
X	page 961, paragraph RESULTS -page 964; figures; tables	1-4, 17-22
	--- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search
[illegible] 2001

Date of mailing of the international search report
[illegible] 2001

Name and mailing address of the ISA
European Patent Office, P.B. [illegible] Patentlaan 2
[illegible]

Authorized officer
[illegible]

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	FIELDS ET AL: "Integrins: cell adhesion molecules in cancer" EXPERT OPINION ON THERAPEUTIC PATENTS.GB,ASHLEY PUBLICATIONS. vol. 8, no. 6, August 1998 (1998-08), pages 633-644, XP002105988 ISSN: 1354-3776	1-22
X	page 636, paragraph 2.2.1 -page 637	1-4, 17-22
Y	CARRON C P ET AL: "A PEPTIDOMIMETIC ANTAGONIST OF THE INTEGRIN ALPHA V BETA 3 INHIBITS LEYDIG CELL TUMOR GROWTH AND THE DEVELOPMENT OF HYPERCALCEMIA OF MALIGNANCY" CANCER RESEARCH.US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 58, May 1998 (1998-05), pages 1930-1935, XP000915219 ISSN: 0008-5472	1-22
X	figure 1 page 1933, paragraph DISCUSSION -page 1935	1-4, 17-22
Y	NICKOLS A ET AL: "ANTIANGIOGENIC AND ANTICANCER ACTIVITIES OF ANTAGONISTS OF INTEGRIN ALPHAVBETA3" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH,US,PHILADELPHIA, AACR, vol. 38, 1 March 1997 (1997-03-01), page 206, abstract no. 1389 XP002071773 abstract	1-22
Y	T J MACDONALD ET AL: "Migration of human brain tumor cells and human brain endothelial cells on tenascin requires the integrin alphaVbeta3:a unifying model for brain tumor invasion and angiogenesis" PROC. ANNU MEET. AACR, vol. 39, 28 March 1998 (1998-03-28), page 497, abstract no. 3382 XP002141915 NEW ORLEANS, LA, MARCH 28 - APRIL 1, 1998,PHILADELPHIA, US abstract	1-22
Y	WO 93 20229 A (GENENTECH INC ;KIM KYUNG	1-22

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	P C BROOKS ET AL: "Requirement of vascular integrin alphaV beta3 for angiogenesis" SCIENCE .AAAS. LANCASTER. PA.US. vol. 264. 22 April 1994 (1994-04-22). pages 569-571. XP002138524 ISSN: 0036-8075 the whole document	1-22
Y	BROOKS P C ET AL: "INTEGRIN ALPHAVBETA3 ANTAGONISTS PROMOTE TUMOR REGRESSION BY INDUCING APOPTOSIS OF ANGIOGENIC BLOOD VESSELS" CELL,US,CELL PRESS, CAMBRIDGE, NA. vol. 79, no. 7, 30 December 1994 (1994-12-30), pages 1157-1164. XP000652129 ISSN: 0092-8674 page 1158 page 1160. paragraph DISCUSSION -page 1162	1-22
Y	VARNER J A ET AL: "TUMOR ANGIOGENESIS AND THE ROLE OF VASCULAR CELL INTEGRIN ALPHAVBETA3" IMPORTANT ADVANCES IN ONCOLOGY,LIPPINCOT-RAVEN, PHILADELPHIA,US, 1996, pages 69-87, XP000857371 ISSN: 0883-5896 page 76. paragraph ALPHAVBETA3 -page 80, left-hand column, line 3	1-22
Y	VARNER J A ET AL: "INTEGRINS AND CANCER" CURRENT OPINION IN CELL BIOLOGY,GB,CURRENT SCIENCE, LONDON. vol. 8, no. 5, October 1996 (1996-10). pages 724-730. XP000857374 ISSN: 0955-0674 * page 728. paragraph Regulation of apoptosis by integrins * page 371. right-hand column. last paragraph -page 373	1-22
Y	VARNER J A ET AL: "REVIEW: THE INTEGRIN ALPHAVBETA3: ANGIOGENESIS AND APOPTOSIS" CELL ADHESION AND COMMUNICATION,US,HARWOOD ACADEMIC PUBLISHERS. GMBH. YVERDON. vol. 3. no. 4. 1995. pages 367-374. XP000857373	1-22

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	GASPARINI G.: "The rationale and future potential of angiogenesis inhibitors in neoplasia" DRUGS, vol. 58, no. 1, July 1999 (1999-07), pages 17-38, XP001002355 abstract page 23, left-hand column page 26, left-hand column page 27; table 1 page 32, left-hand column	1-22
Y	DAMIANO JS ET AL: "Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines." BLOOD, vol. 93, no. 5, 1 March 1999 (1999-03-01), pages 1658-1667, XP002168941 abstract paragraph 'DISCUSSION!	1-22
Y	UHM, JOON H. ET AL: "Vitronectin, a glioma-derived extracellular matrix protein, protects tumor cells from apoptotic death" CLIN. CANCER RES., 06-1999, VOL. 5, NO. 6, PAGE(S) 1587-1594, XP002168942 abstract figures 2,3 page 1592, paragraph DISCUSSION -page 1594	1-22
Y	MUELLER, B. M. ET AL: "Pre-clinical therapy of human melanoma with morpholino-doxorubicin conjugated to a monoclonal antibody directed against an integrin on melanoma cells" ANTIBODY, IMMUNOCONJUGATES, RADIOPHARM., 1991, VOL. 4, NO. 2, PAGE(S) 99-106, XP001002266 abstract figures 1,3-5 table 1	1-22
Y	BITAN GAL ET AL: "Mapping the integrin alphaVbeta3-ligand interface by photoaffinity cross-linking." BIOCHEMISTRY ISSN: 0006-2960 abstract figure 1	1-22

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
Y	SHEU JOEN R ET AL: "Triflavin, an arg-gly-asp-containing peptide, inhibits the adhesion of tumor cells to matrix proteins via binding to multiple integrin receptors expressed on human hepatoma cells." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, vol. 213, no. 1, 1996, pages 71-79. XP001002230 ISSN: 0037-9727 abstract	1-22

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-22 in part

Present claims 1-22 relate to a conjugate, a method for its preparation, and its use.
Part of the conjugate is defined by reference to a desirable characteristic or property, namely its affinity for "an alpha-v,beta-3 integrin receptor". Although structural features are given to "define" this part, these features contain so many options, variables, possible permutations and provisos, that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.
This same applies to the definition of the linker group. Moreover, the linker group in the claims is defined in reverse order when compared to the examples, which leads to confusion.
The definition of the "cytotoxic radical or a radical of a cytostatic or of a cytostatic derivative" relates to an extremely large number of possible radicals. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only one single of the radicals claimed, camptothecin. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the conjugates prepared in the examples, and to the idea of targeting an anticancer agent to integrin receptors.
This initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.
Consequently, the search has been further restricted to the conjugates prepared in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 00/08361

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320229 A	14-10-1993	AT 175241 T	15-01-1999
		AU 680411 B	31-07-1997
		AU 3941393 A	08-11-1993
		CA 2132091 A	14-10-1993
		DE 69322860 D	11-02-1999
		DE 69322860 T	01-07-1999
		EP 0633945 A	18-01-1995
		JP 7505528 T	22-06-1995
		US 5578704 A	26-11-1996
		US 5652109 A	29-07-1997
		US 5652110 A	29-07-1997

PATENT COOPERATION TREATY

PCT

REC'D 21 NOV 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

12

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
LEA33861-WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08361	28/08/2000	08/09/1999
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant BAYER AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report

preliminary examining authority:
European Patent Office
D-80298 Munich

Vogt, T

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08361

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-203 as originally filed

Claims, No.:

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

[illegible] considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-22.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-22.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

III No opinion.
See the international search report.

IV Lack of unity of invention (Rule 13 PCT).
Claim 1 describes a conjugate comprising a targeting agent, a hydrolysable linker and a cytostatic agent, characterized in that the targeting agent is a non-peptide moiety.

Claim 4 relates to three conjugates A, B and C which differ from each other in the targeting group.

The linking concept between the compounds of claim 4 is the general formulation of claim 1, and the general formulation of the linker group and the cytostatic agent.

The general concept of drug targeting using conjugates with a targeting agent, a hydrolysable linker and a cytotoxic agent is long known and already widely applied. D13 is an example of such an application. The difference between D13 and present application is the use of an monoclonal antibody vs. a non-peptide moiety and the use of a cytotoxic vs. a cytostatic compound.

The targeting groups depicted in claims 4A-C are known from the prior art (cf. the long list of patent applications on p. 42 and 43). The use of cytotoxic or cytostatic agents, and hydrolysable linkers (including those for use in ADEPT strategy) in drug targeting conjugates is well known to the skilled artisan.

Hence, the applicant merely exchanged one well known targeting agent for another. This is not considered to comprise an inventive step, especially since the advantages of such an exchange can be anticipated in advance.

The examiner therefore identifies three inventions, represented by claim 4A-C, and all claims dependent thereon.

Reasoned Statement (Rule 66.2 [illegible]
subject matter of the present application

The provision of a conjugate comprising a targeting group, a hydrolysable linker, and a cytostatic agent, characterized in that the targeting group is a non-peptide, a process to prepare said conjugates and the use thereof in the preparation of medicaments.

Cited prior art documents (Rule 64(1) PCT).

D1: KERR ET AL. (1999) ANTICANCER RES. 19, 959-968.
D2: FIELDS ET AL. (1998) EXP. OPIN. THER. PATENTS. 8, 633-644.
D3: CARRON ET AL. (1998) CANCER RES. 58, 1930-1935.
D4: NICKOLS ET AL. (1997) PNAS 38, 206, abstract no. 138.
D5: MACDONALD ET AL. (1998) PROC. AMER. ASSOC. CANCER RES. 39, 497.
D6: BROOKS ET AL. (1994) CELL 79, 1157-1164.
D7: VARNER ET AL. (1996) IMP. ADV. ONCOL., 69-87.
D8: VARNER ET AL. (1996) CURR. SCIENCE 8, 724-730.
D9: VARNER ET AL. (1995) CELL ADH. COMM. 3, 367-374.
D10: GASPARINI (1999) DRUGS 58, 17-38.
D11: DAMIANO ET AL. (1999) BLOOD 93, 1658-1667.
D12: UHM ET AL. (1999) CLIN. CANCER RES. 5, 1587-1594.
D13: MUELLER ET AL. (1991) ANTIBODY, IMMUNOCONJUG., RADIOPHARM. 4, 99-106.
D14: BITAN ET AL. (1999) BIOCHEMISTRY 38, 3414-3420.
D15: SHEU ET AL. (1996) PROC. SOC. EXP. BIOL. MED. 213, 71-79.
D16: WO 93 20229 A
D17: BROOKS ET AL. (1994) SCIENCE 264, 569-571.

Added by the examiner:
D18: Teicher et al. (1996) Cancer Chemother. Pharmacol. 38, 169-177.

The prior art documents mainly relate to the importance of the integrin $\alpha_v\beta_3$ in the tumour induced angiogenesis (see D5-D9). It is reported that inhibition of said integrin with antibodies (D16), peptides comprising the RGD sequences (D2, D15), peptidemimetics (D3, D4), and non-peptidic compounds (D1, D2) leads to a regression of tumour growth. All cited documents contain incentives to design drugs specifically

D2 is a review in which several non-peptide ligands for $\alpha_v\beta_3$ are mentioned. (cf. §2.2.1.

and the references cited therein).

D13 appears particularly important as it discloses the application of the general concept of drug targeting using a conjugate comprising a monoclonal antibody, a hydrolysable linker and a cytotoxic agent. It shows that the conjugate comprising the Ala_3 linker is more active then the same amount of individual compounds alone, or compositions comprising all the individual compounds. A striking observation made by D13 was the difference between the activity of the conjugates relative to the parental compounds in-vitro and in-vivo tests. D13 shows that the Ala_3-conjugate performs particularly well in in-vivo tests (cf. Results and Discussion sections).

D14 discloses another variant of compound targeting, namely the targeting of a photo-affinity label to $\alpha_v\beta_3$ using an RGD comprising cyclic peptide as the targeting agent. The aim of D14 was however, not to design a medicament but to explore the surface of the binding site of $\alpha_v\beta_3$.

D18 discloses pharmaceutical compositions comprising an antiangiogenic agent (eg. tnp-470) and a cytotoxic agent (eg. cyclophosphamide, adriamycin). The closing conclusion of D18 is that the combined application of an antiangiogenic agent and a cytotoxic agent may interact in a positive way, it is stated: 'Perhaps the important factor in translating these findings to clinical studies is that the addition of antiangiogenic agents to treatment (of solid tumours, ex.) is most likely to make very good therapeutic regimens better' (p. 174, Discussion).

Novelty (Art. 33(2) PCT).

Since none of the cited prior art documents disclose the use of non-peptide ligands in drug targeting conjugates the novelty of the subject matter is acknowledged.

Inventive step (Art. 33(3) PCT).

The difference between D13 and the present application is the use of non-peptidic targeting agents. The problem solved by the applicant appears therefore to be the provision of an alternative targeting agent for use in drug targeting conjugates.

D2 for a short review). Hence, to provide an alternative to the monoclonal antibodies of

D13 the skilled artisan has a limited number of possibilities. The choice for non-peptidic compounds is an obvious choice as the advantages can be anticipated in advance, and a large variety of such compounds have already been disclosed (cf. p. 42-43 of the description, D1 and the references cited in § 2.2.1 of D2).

Furthermore, the properties of the linker are determined by the strategy to be used. The linker of D13 is designed to be hydrolysed by cytosolic enzymes. Other strategies known in the art are based on enzymes specifically secreted by tumour cells. Another known strategy for drug targetting is the use of **A**ntibody **D**irected **E**nzyme **P**rodrug **T**herapy (see for instance Melton et al. (1996) Drugs of the future 21, 167-181, or Bagshawe (1994) J. Controlled Release 28, 187-193 for reviews). The most unspecific linker would be one which is hydrolysable by its chemical nature (eg. di-thio bonds). Also linkers for the attachment of two or more cytotoxic/cytostatic agent are known. All these strategies are known to skilled artisan and none of them, therefore, requires an inventive step.

Finally, the use of cytostatic or cytotoxic agents is common practice in drug targeting. Also the preferred drugs listed in the description are known to skilled artisans as such. So also the drugs used by the present application do not comprise an inventive step.

To conclude, the general concept of drug targeting is long known and the individual components of the conjugates of the present application are also known. Hence, the invention must be found in the combination thereof, especially in the use of known ligands/inhibitors in conjugates for drug targeting.

The examiner is of the opinion that this new use lacks an inventive step, because the advantage of such a use can be anticipated in advance.

Hence, the conjugates of the present application lack an inventive step. Since the process to prepare the conjugates and the use thereof do not contain any features that may confer an inventive step thereto, these are only patentable with a patentable compound claim.

conjugates comprising specific ligands, if these ligands are not known from the prio

art, and 2) the claims are not directed to general formulations.

Industrial applicability (Art. 33(4) PCT).
The conjugates are useful in the treatment of cancer.

VII Defects in the description (Art. 5 PCT).
To meet the requirements of Rule 5 PCT the applicant is requested to identify D2, one of D6 or D17, one of D7-D9, D13 and D18.

Viii Clarity of the claims (Art. 6 PCT).
Claims 1-3 are written as 'results to be achieved'. The applicant should reformulate said claim and incorporate therein the technical features necessary to achieve the desired result (Guidelines C-III, 4.7).

The claims encompass such a huge amount of possible conjugates that it would be an undue burden on the skilled artisan to determine the true scope of the claims (eg. those that actually fulfill the requirements laid down in claim 1). The applicant should therefore restrict the scope of the claims to those conjugates for which it can be unmistakenly deduced that they fulfill all the requirements of claim 1 (Art. 6 PCT).